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Formal Total Syntheses of Aspidosperma Alkaloids via a Novel and General Synthetic Pathway Based on an Intramolecular Heck Cyclization

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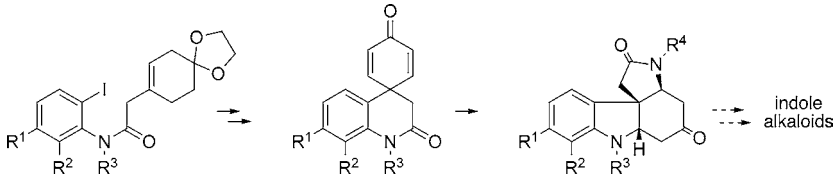
ABSTRACT



Cyclizations of bicyclic amides via an intramolecular Heck reaction followed by an oxidation reaction generate tricyclic spirocyclohexadienones. From these compounds, tetracyclic ketones can be synthesized to provide useful intermediates for the synthesis of indole alkaloids.

Indole alkaloids are an important class of natural products especially as many members of this family display a wide range of biological activities. These properties include antitumor,[1] adrenergic blocking,[2] and glycine antagonist[3] activities. Such alkaloids are exemplified by strychnine **1**,[4] tubifoline **2**, aspidospermine **3a**,[5] vindoline **4** and the clinically used anticancer drug agents vinblastine **5** and vincristine **6**, which are produced in extremely small quantities in the plant *Vinca rosea* (Figure 1).[6]

The [6.5.6.5] ABCE ring system **7** is the common scaffold of indole alkaloids. Several approaches have been developed to synthesize this skeleton based on the chemistry of free radicals, of tandem radical cyclization,[7] of palladium−catalyzed asymmetric allylic substitution,[8] of skeletal rearrangement of a 3-chloroindolenine,[4] of an intramolecular

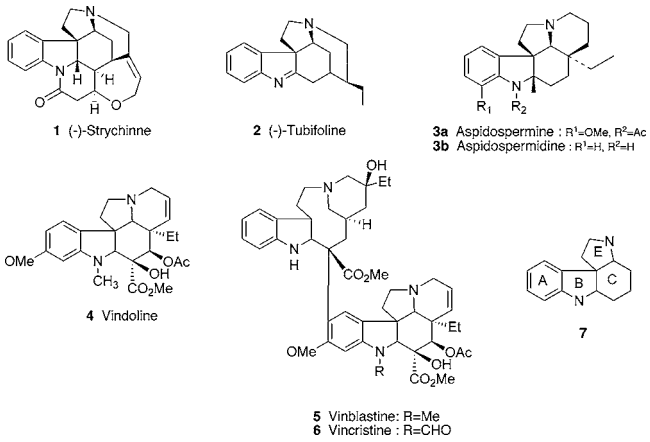


Figure 1. Aspidosperma alkaloids.

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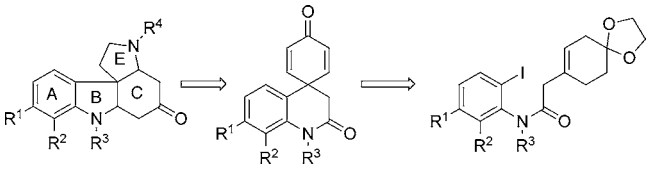
Diels−Alder reaction,[9] of catalyzed polycyclization,[10] or of tandem Mannich condensation followed by a [3,3]-sigmatropic rearrangement.[11]

The indole alkaloids display a spiro quaternary carbon. The incorporation of this quaternary center is the critical element in the total synthesis of indole-type alkaloids. We previously reported the use of an intramolecular Heck reaction as an alternative for creating the spiro quaternary center of the Amaryllidaceae galanthamine-type[12] and maritidine-type[13] alkaloids.

In our synthetic pathway, we planned to use an intramolecular Heck reaction to access spirotricyclic dienones **9**, which can provide the tetracyclic ketones **8** as key intermediates in the synthesis of indole alkaloids and their analogues (Scheme 1). The intramolecular Heck reaction has rarely been

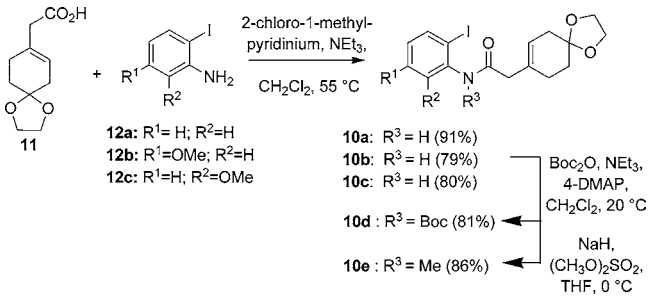
Scheme 1. Retrosynthesis of Ketones **8**



8 **9** **10**

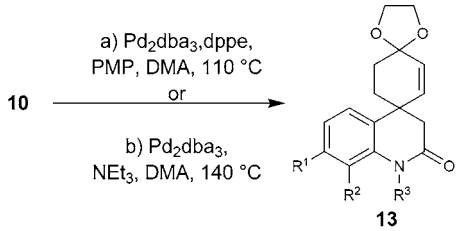
applied to anilides to access spirodihydroquinolones.[14] The diastereoselective construction of the common [6.5.6.5] ABCE scaffold **8** started with acid **11**[15] and anilines **12**,[16] which were coupled to furnish the corresponding anilides **10** in satisfactory yields (Scheme 2).

Scheme 2. Synthesis of the Anilides **10**



Heck cyclizations of **10** were accomplished in the presence or absence of phosphine ligands in dimethylacetamide (Table

Table 1. Heck Cyclizations of **10**



a) Heck conditions ; b) Ligand Free Heck conditions

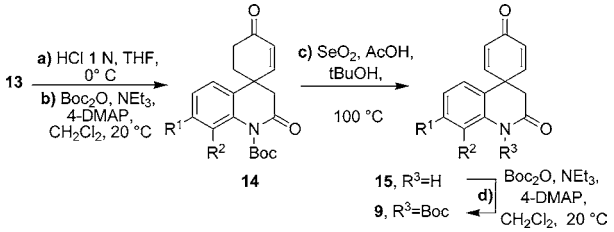
precursor	R^1	R^2	R^3	products	Heck yield[a] (%)	Heck free yield[a] (%)
10a	H	H	H	**13a**	52	92
10b	OMe	H	H	**13b**	88	87
10c	H	OMe	H	**13c**	94	86
10d	H	OMe	Boc	**13d**	96	nd[b]
10e	H	OMe	Me	**13e**	80	nd[b]

[a] Isolated yield after column chromatography. [b] Not determined.

1). Under "ligand-free" conditions the yield of **13a** was greatly increased (92%) while the yield of **13b** remained unchanged and the yield of **13c** decreased (Table 1).

After hydrolysis of the dioxolane group of **13** with hydrochloric acid and protection of the amide function with Boc_2O, oxidation of the α,β-unsaturated ketone function of the resulting product **14** to the corresponding dienones **15** was accomplished by using selenium dioxide and acetic acid in ^{t}BuOH. The amine function was then reprotected with Boc group to give compounds **9a**−**c** (Table 2).

Table 2. Synthesis of the Spirodienones **9**



precursor	product	overall yield (%)
13a: $R^1 = R^2 = H$	**9a**	62
13b: $R^1 = OMe$; $R^2 = H$	**9b**	58
13c: $R^1 = H$; $R^2 = OMe$	**9c**	68

With a ready access to the three key spirodienone precursors, we next turned our attention to the crucial lactam

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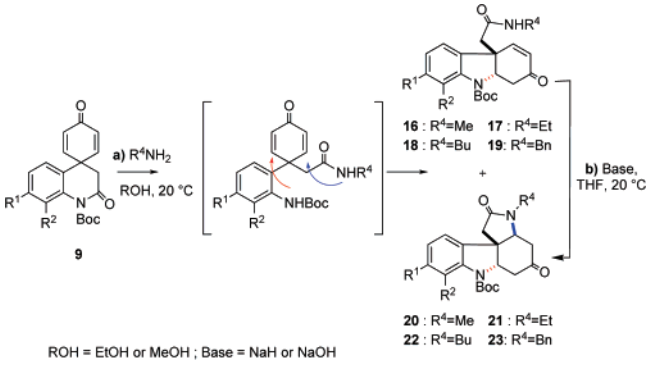
(15) For preparation of acid **11**, see ref 13.

opening. Previous attempts at such conversions have been unsuccessful.[17] However, in our hands reaction of anilides **9** with different primary amines provided the corresponding mixtures of tricyclic compounds **16**−**19** by a Michael addition and tetracyclic compounds **20**−**23** by a double Michael addition. These mixtures were subjected to basic cyclization in the presence of sodium hydride or sodium hydroxide to yield only the tetracyclic products **20**−**23** (Table 3). Compounds **20**−**23** are interesting scaffolds for the synthesis of N-substituted and A-modified ring analogues of indole alkaloids.

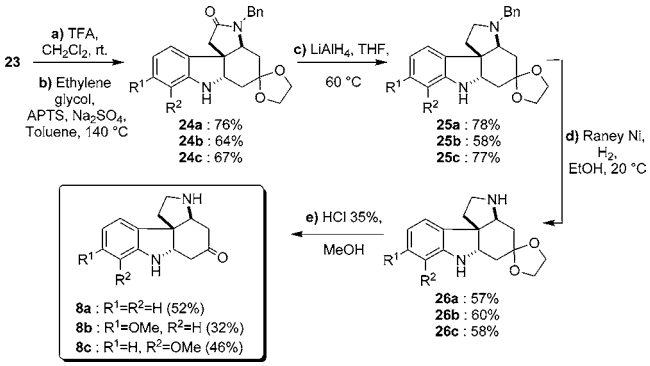
Table 3. Preparation of Tetracyclic Compounds **20**−**23**



precursor	products	yield (%)
9a: $R^1 = R^2 = H$	**20a**, $R^4 = Me$	68
	21a, $R^4 = Et$	35
	22a, $R^4 = Bu$	48
	23a, $R^4 = Bn$	79
9b: $R^1 = OMe$; $R^2 = H$	**20b**, $R^4 = Me$	66
	21b, $R^4 = Et$	27
	22b, $R^4 = Bu$	30
	23b, $R^4 = Bn$	73
9c: $R^1 = H$; $R^2 = OMe$	**20c**, $R^4 = Me$	74
	21c, $R^4 = Et$	63
	22c, $R^4 = Bu$	64
	23c, $R^4 = Bn$	70

At this stage, all that remained to complete the synthesis of the tetracyclic core of the *Aspidosperma* and *Strychnos* alkaloid families was the reduction of the pentacyclic amide function. This reduction can be accomplished after deprotection of the aniline function of **23** and protection of the ketone by a dioxolane group to yield **24**. The deprotection of the aniline was realized before the protection of the ketone function to optimize the yield (Scheme 3).

Scheme 3



Finally, the amide functions of **24a**−**c** were reduced with lithium aluminum hydride to afford the corresponding amines **25**, which were subsequently subjected to N-debenzylation and deprotection of the ketone. Compounds **8a**−**c** were thus obtained in satisfactory yields.

In summary, we have developed an efficient and diastereoselective methodology that enables the construction of a large series of tetracyclic indolino derivatives **20**−**23**, **25**, and **8**, which correspond to the cores of the *Aspidosperma* and *Strychnos* alkaloids as well as their analogues. The approach is based on two key steps: an intramolecular Heck cyclization applied to anilides and a lactam opening−Michael addition reaction. Current efforts are now directed toward developing an enantioselective version and application to the synthesis of natural indole alkaloids.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Aniline **12a** is commercially available. (b) For preparation of **12b**, see: Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507. For preparation of **12c**, see: Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117.

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